SMALL CELL CARCINOMAS OF THE LUNG*

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With the increasing number of reports upon primary carcinoma of the lung, views as to classification have changed. Classification upon the basis of gross morbid anatomy has been largely abandoned because of wide variations in form, which overlap the classes, apparently as the result of local extensions and regional metastases. Classification as to point of origin is unsatisfactory because there have been no convincing demonstrations of origin from any part of the lung other than bronchi and bronchioles.

Classification upon the basis of the histological character is not without its difficulties, but is more satisfactory than the other two modes. Squamous epitheliomas and adenocarcinomas can be readily identified. Even when the epitheliomas show no keratinization the other features are usually sufficient for a diagnosis. Often the adenocarcinomas show only a few areas of acinus formation, which may not be found in only a single section. Of the undifferentiated cancers some are made up of polygonal, cuboidal or cylindrical cells and can only be called carcinoma simplex. Others show a curious tendency to the formation of bizarre multinucleated giant cells, but it is doubtful that these justify a separate classification because such cells are found in undifferentiated and differentiated tumors of our series. Most common among the undifferentiated forms are those cancers which have been called transitional cell, oat-cell and small cell carcinomas.

Practically without exception this last group of tumors is made up of small spindle cells and small round cells, one or the other predominating in different parts of the tumor and its metastases. In the spindle cell areas a certain degree of nuclear palisading is noted but not with the same regularity of arrangement commonly seen in the neurofibroma (Schwannoma). The cells are likely to be grouped in large nests, bounded by irregular, well vascularized septa of mature

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connective tissue, and the tumor is thus said to be alveolated. In the midst of the cell masses there may be a papilliform strand of connective tissue fibers with one or two thin-walled blood vessels and the tumor cells appear to grow in parallel bundles from this fibrous tissue. Nuclear character varies greatly. The spindle cells usually have vesicular nuclei and the round cells usually densely chromatic nuclei, but the reverse may be true. Mitotic figures are not commonly abundant.

Ewing's [1] article on lymphoepithelioma describes tumors of the nasopharynx which histologically resemble transitional cell carcinoma, but the structure of bronchi and bronchioles gives no ground for assuming that the small cell cancers of the lung belong in the group of lymphoepithelioma.

Only within recent years have the small cell tumors of the lung been accepted as cancers, although Turnbull, who has seen an extraordinary number of lung tumors at The London Hospital, is quoted by Simpson [2] as having been of this opinion for many years. That they are not sarcomas has been concluded because of cellular arrangement, vascularization, connective tissue relations, gross characters resembling obvious carcinomas and distribution of metastases.

The subject is of interest in connection with the Schneeberg lung cancers. Clinically the disease was described in 1770 (see Uhlig[3]). In 1879 Härting and Hesse described cases which came to autopsy. Schmorl [4] states that these were considered to be lymphosarcoma by Wagner, by Weigert and by Anke. Arnstein [5] pointed out clearly that the small cell metastases of his case were epithelial. Schmorl quoted Uhlig as having demonstrated that one of the Härting-Hesse cases was a small cell carcinoma and the other was combined with an "Endothelkrebs." With this background the impression has apparently been gained that the Schneeberg tumors are commonly of the small cell type. Schmorl's examination of twenty-one Schneeberg lung cancers showed that only three of them were small cell cancers.

In some clinics the small cell tumors constitute the majority of the lung cancers, but in others their number is exceeded by the squamous epitheliomas. Of twenty-five cases of primary carcinoma of the lung observed by us at City and Lakeside Hospitals, demonstrated by complete autopsy, thirteen were squamous epitheliomas,

six were small cell carcinomas, four were adenocarcinoma and two were classified as carcinoma simplex.

It is at least possible that the study of primary carcinoma of the lung may be advanced by detailed examination of the different forms encountered. For this purpose the cases of small cell carcinoma have been selected. The information provided by Weller [6] and by Simpson provides us with data for larger comparison.

Primary cancer of the lung occurs between 20 and 80 plus years, with the greatest incidence between 50 and 60 years. In our twenty-five cases the ages were between 38 and 76 years. The small cell cancers occurred between 40 and 72 years, distributed at 40, 41, 41, 58, 64, 72 years. There is then no striking change of age incidence.

Although statistics differ, in general it may be said that the sex ratio of primary cancer of the lung is four males to one female. In our cases of small cell carcinoma four were in males and two in females.

Of our twenty-five cases nineteen were in whites and six were in negroes. Of the small cell cancers, five were in whites and one in a negro.

Duration of symptoms is based upon much human uncertainty. In Simpson's 139 cases, the average duration was seven months. Only seven lived more than two years and two more than four years. In our twenty-five cases, the duration was ten days to two and a third years. In the small cell cancer cases it was three weeks to two years.

Generally it is found that the right lung is involved slightly more often than the left. In one of our six cases of small cell carcinoma, the lesion was discovered microscopically and the side not identified. Of the others, three were on the right side and two on the left.

A study of occupation and symptoms shows nothing in which the small cell cancers differ materially from the others. Moderate anemia, leucocytosis, fever, cough, weakness, anorexia, dyspnea, hemoptysis and pain in the chest were present about equally in both groups.

The correct clinical diagnosis was made in ten of the twenty-five cases, but in the cases of small cell cancers in only one of six instances. In one of these cases it was not to be expected that the diagnosis should be made because the tumor was only about 5 mm. in diameter.

Grossly, with the possible exception of the tumor discovered microscopically, all the small cell cancers were situated at the hilum. Two showed multiple small nodules throughout the lung. The other three were masses 6 to 12 cm. in diameter near the hilum. One case showed extensive bronchiectasis and one showed an area of necrosis (not gangrenous) 6 to 8 cm. in diameter, distal to the tumor. Generally, the tumors were of gray color, clearly invasive, firm, cut with resistance and showed a firm, pale gray or yellowish gray, moist cut surface. Vascularization was not marked and hemorrhage not noteworthy. Necrosis occurred in the larger masses as it did in carcinoma in general.

Extrathoracic metastases were proportionately more frequent in our small series of small cell cancers than in the others. Especially notable is the fact that whereas four of the nineteen other cancers showed extensive mediastinal metastasis, three of the six small cell cancers showed marked involvement of that region. Two of these were diagnosed clinically as mediastinal sarcoma. The situation in our cases, as is true of such tumors generally, was especially in the upper posterior mediastinum with anterior displacement of the trachea. This type of metastasis has been emphasized by others and Barnard [7] goes so far as to state that "the so-called 'oat-celled sarcoma' of the mediastinum is a medullary carcinoma of bronchi." Shennan [8] describes thirteen cases of small cell cancer of the lung, one of which (No. 8) is not entirely acceptable to us as of this category. All of these showed some degree of mediastinal involvement and in seven of them it was marked. Duguid and Kennedy [9] conclude "that oat-cell forms in a mediastinal tumor must not always be interpreted as indications of bronchial origin," and report one case originating in a thymic tumor and one originating in the mediastinal lymph nodes. Schuster,[10] without publishing the figures, states that "there is no relation between the type of growth and the size of the mediastinal mass." Maxwell [11] in a series of 239 cases of primary malignant tumor in the thorax, of which 135 were examined microscopically, found forty-seven cases of "obvious" carcinoma and sixty-four cases of oat-cell tumor. Mediastinal involvement was found in about 60 per cent of the small cell tumors as compared with about 55 per cent of the other cancers. Huguenin [12] speaks of "tumeurs médiastino-pulmonaires qui se présentent fréquemment sous l'aspect de tumeurs à petites cellules." It is probable

therefore that mediastinal involvement is somewhat more frequent in connection with the small cell cancers than is true of other cancers of the lung.

Discussion of the origin of primary cancers of the lung has been of particular importance as concerns the small cell tumors, for this is the type which Huguenin thought to be derived from alveolar lining. Weller, in his review, states that "proof of the origin of carcinoma of the lung from histologically unaltered alveolar epithelium is lacking." Subsequently Schuster concluded that "the existence of alveolar carcinoma is not proven." Maxwell, referring to the sixty-four small cell carcinomas he studied, states that "it has not been shown that any of the tumors in this series arose directly in the epithelial lining of the pulmonary alveoli." Huguenin, Foulon and Delarue,[13] as well as Huguenin, appear to admit some doubt as to Huguenin's original contention. All writers on this subject hope for what Weller calls the "fortuitous discovery of early examples in the course of routine autopsies," or the "hazard heureux de coupe" of Huguenin. Certainly the modern literature shows agreement with Weller that cell type of the tumor is not a criterion of point of origin.

Figs. 1, 2, 3 and 4 are from a small cell cancer found by Dr. Alan Moritz in the routine sections of the lung in a case of chronic diffuse bronchiectasis. In addition to masses of oval cells in the lung tissue a large space shows a lining of multiple layers of cells of the same type. That this space is not alveolar is indicated by the fact that its walls contain much smooth muscle, as shown by the round ended cylindrical nuclei. The Van Gieson technique shows many yellow-stained fibrils in the wall and the Verhoeff elastica stain several layers of elastic fibrils in irregular arrangement. The Mallory connective tissue stain shows spaces between the connective tissue fibrils. It must be a bronchiole. A slightly larger bronchiole shows squamous metaplasia without keratinization. It is probable, but not proved, that the multiple layers of oval cells represent a diffuse proliferation, but this does not exclude the possibility of extension of the cancer over the bronchiolar surface. No other focus of origin could be found in many sections, nor could a similar multiplication of layers be found in any of the clearly distinguishable alveoli. The Bielschowsky-Foot stain [14] (Fig. 2) shows no reticulum in the surface cells or in the deep cancer nodules. The origin of this lesion appears to be in a bronchiole and not in a bronchus with cartilaginous

walls. Huguenin has suggested that origin from a bronchiole might easily be confused subsequently with origin from alveolar lining cells.

The problem of multicentric or unicentric origin is not solved by this observation. The bronchiolar surface involved is about 1 mm. in length. To this extent the origin appears to be somewhat diffuse as compared to the possibility of origin in a few cells. If multicentric in this instance, the number of centra must be small. Broadly speaking, this tumor can be regarded as unicentric. The examination of our entire series of lung carcinomas indicates that they originate in a bronchus or bronchiole and that multiplicity of tumors in the same lung is the result of metastasis rather than multicentric origin. This view is supported by the early invasion of lymphatics, frequent invasion of veins and occasional invasion of arteries, common to lung cancers.

The gross morbid anatomy of small cell carcinomas of the lung differs from that of other carcinomas of the lung in only two particulars. The small cell cancers are generally somewhat firmer and show a slightly greater disposition to produce large mediastinal masses than the other cancers.

Microscopically, in addition to cell type, the vascularization and desmoplastic activity of the small cell cancers is striking. The blood vessels are numerous in the pulmonary and metastatic tumors. They have thin walls, with little or no musculature and appear in delicate or heavy bands of connective tissue throughout the tumor masses. The bare capillaries or vascular slits of sarcoma are not found. With the Van Gieson stain the amount of fibrous connective tissue is seen to be in excess of what might be expected from viewing the same tissue stained with hematoxylin and eosin. Not only are there heavy bands which give the tumor an alveolated appearance, but within the tumor cell masses are many more or less delicate short or long bundles. As compared with other cancers of the lung, the amount of connective tissue in the small cell cancers appears to be greater and its distribution more diffuse.

Three of our small cell cancers have been stained with the Foot modification and one with the Maresch modification of the Bielschowsky technique. Whereas the cell masses show fibrils of connective tissue, they are devoid of reticulum. This is entirely independent of rapidity of growth as judged by clinical history or gen-

eral appearance of the tumor. In no instance were reticulum fibrils found except as occasional strands connected with the reticulum of the surrounding host tissue. There is no indication whatever that the tumor cells have any capacity to form reticulum. This demonstration is in accord with that made as early as 1913 by Arnstein. Although rapidly growing sarcomas may be poor in reticulum, the lymphatic group, with which the small cell cancers have been confused, usually show a striking tendency in this direction, in sharp contrast to the small cell cancers.

The cells of the tumor appear in masses which resemble pure cultures of the cells (Huguenin). This appearance is conspicuous in hematoxylin-eosin and Bielschowsky preparations, but in Van Gieson preparations the illusion is destroyed by the presence of the connective tissue fibrils. Parallel rows of oval or spindle cells are attached to the denser connective tissue bands. These are continuous with masses of round cells or of spindle or oval cells which often occur in bundles with a certain suggestion of palisading of nuclei. There is no reason for suspecting that the round cells are simply cross-sections of spindle cells because they occur in large masses without spindle cells in association. The fact that areas of tumor necrosis are usually surrounded by round cells and that densely chromatic small nuclei, probably pyknotic, are frequent in the round cells suggests that some of these cells are the seat of regressive pathological change. Thus, they may be regressive forms of other round cells or of spindle cells. Variability of nuclear staining is a notable feature of both spindle and round cells. Nuclei may appear to be vesicular or densely chromatic. Since the nuclei of bronchiolar epithelium and the connective tissues stain normally in the sections it is probable that the tumor cell nuclei vary in chromatin content as indicated by the staining. In a specimen removed by the bronchoscope, the same irregularity of nuclear character was observed. No autopsy was permitted in this case and although the diagnosis was practically certain the case is not included in our series. Admitting it as a small cell cancer of the lung excludes the irregularity of nuclear staining as a postmortem change. The nuclei of the round cells are of the order of twice the diameter of an erythrocyte. Those of the spindle cells are of the order of one erythrocyte in width and two erythrocytes in length. Multiple nuclei are infrequent. The few mitotic figures observed are not abnormal.

Although others have observed a considerable differentiation of the cells, only one of our cases showed in one field cells which could be regarded as cuboidal or low cylindrical. Generally speaking, these small cell tumors show little or no further differentiation.

Conclusions

1. Small cell primary tumors of the lungs or bronchi are epithelial in character, as indicated by cell arrangement, relation of connective tissues and blood vessels, and complete absence of capacity to form reticulum.

2. Small cell cancers of the lung originate in bronchi or bronchioles and are probably unicentric in origin.

3. Small cell cancers of the lung more frequently produce large mediastinal masses than do other cancers of this organ and are firmer in consistency, but in other clinical and gross pathological aspects show no distinctive characters.

REFERENCES

1. Ewing, J. Lymphoepithelioma. *Am. J. Path.*, 1929, 5, 99.
2. Simpson, S. L. Primary carcinoma of the lung. *Quart. J. Med.*, 1929, 22, 413.
3. Uhlig, M. Ueber den Schneeberg Lungenkrebs. *Virchows Arch. f. path. Anat.*, 1921, 230, 76.
4. Schmorl, G. (See Rostoki and Saupe.) Die Bergkrankheit der Erzbergleute in Schneeberg in Sachsen ("Schneeberger Lungenkrebs"). *Ztschr. f. Krebsforsch.*, 1926, 23, 360.

   Thiele, Rostoki, Saupe and Schmorl. Ueber den Schneeberger Lungenkrebs, *München med. Wchnschr.*, 1924, 71, 24.
5. Arnstein, A. Ueber den sogenannten "Schneeberger Lungenkrebs." *Verhandl. d. deutsch. path. Gesellsch.*, 1913, 16, 332; *Wien. klin. Wchnschr.*, 1913, 26, 752.
6. Weller, C. V. The pathology of primary carcinoma of the lung. *Arch. Path.*, 1929, 7, 478; Entdifferentiation in primary carcinoma of the bronchi and lungs. *J. Cancer Research*, 1929, 13, 218; The pathology of certain signs and symptoms in primary carcinoma of the lung: illustrative cases. *Ann. Int. Med.*, 1929, 2, 725.
7. Barnard, W. G. The nature of the "oat-celled sarcoma" of the mediastinum. *J. Path. & Bact.*, 1926, 29, 241.
8. Shennan, T. Tumours of mediastinum and lung. *J. Path. & Bact.*, 1928, 31, 365.
9. Duguid, J. B., and Kennedy, A. M. Oat-cell tumours of mediastinal glands. *J. Path. & Bact.*, 1930, 33, 93.
10. Schuster, N. H. Aetiology and pathology of primary lung tumours. *J. Path. & Bact.*, 1929, 32, 799.
11. Maxwell, J. Primary malignant intrathoracic tumours. *J. Path. & Bact.*, 1930, 33, 233.
12. Huguenin, R. Les aspects histologiques des cancers primitifs du poumon. *Ann. d'Anat. Path. et d'Anat. Norm.*, 1929, 6, 241.
13. Huguenin, R., Foulon, P., and Delarue, J. Le revêtement de l'alvéole pulmonaire ses destinées pathologiques. *Ann. d'Anat. Path. et d'Anat. Norm.*, 1929, 6, 775.
14. Foot, N. C. Technic for demonstrating reticulum fibers in Zenker-fixed paraffin sections. *J. Lab. & Clin. Med.*, 1924, 9, 777. See also McClung, C. E., Handbook of Microscopical Technique, New York, 1929, 294.
15. Foot, N. C., and Day, H. A. The occurrence of reticulum in tumors. *Am. J. Path.*, 1925, 1, 431.

DESCRIPTION OF PLATES

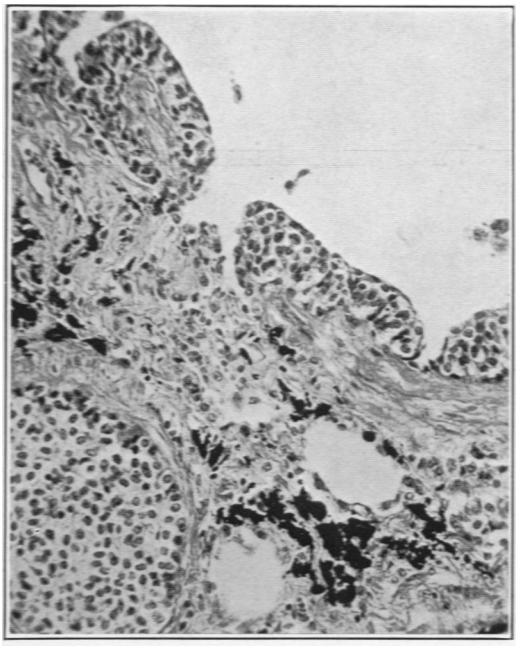
PLATE 118

FIG. 1. Multiplication of bronchiolar epithelium and nodule of small cell carcinoma deeper in the tissue. Hematoxylin and eosin. Green filter, Wratten B 58. × 200.

FIG. 2. Same material as in Fig. 1, stained by the Bielschowsky-Foot method. Note absence of reticulum in the epithelial areas. Orange filter, Wratten G 15. × 200.

FIG. 3. Same material as Fig. 1, stained by the Verhoeff elastica method. Note the irregular distribution of fibrils, different from that of an artery. Red filter, Wratten A 25. × 200.

FIG. 4. Same material as Fig. 1, stained by the Mallory connective tissue stain. Note the wide spaces between the fibrils in the subepithelial tissue. The spaces are occupied by smooth muscle as demonstrated by the Van Gieson method. Green filter. × 200.



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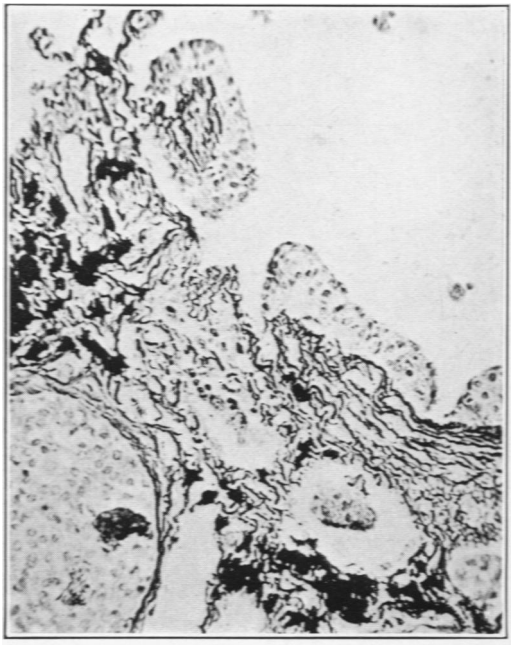

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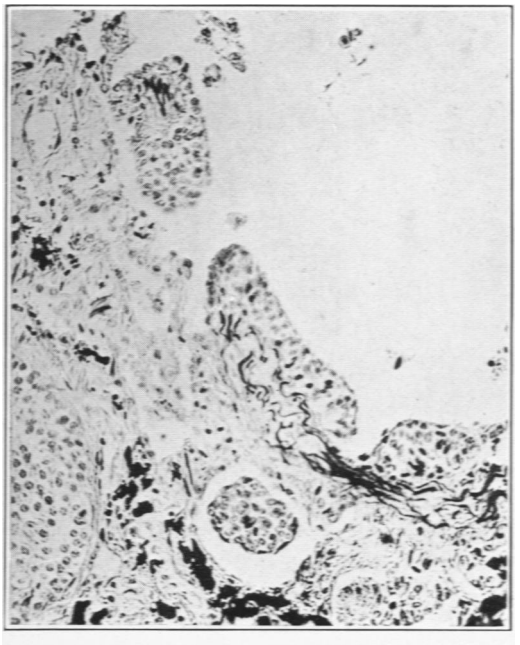

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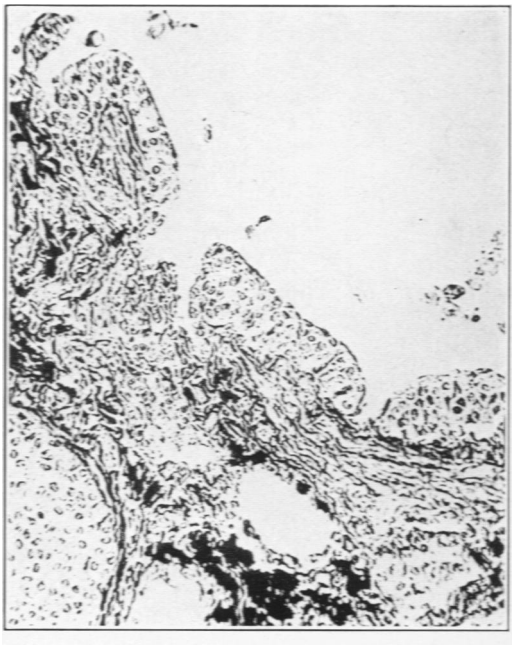

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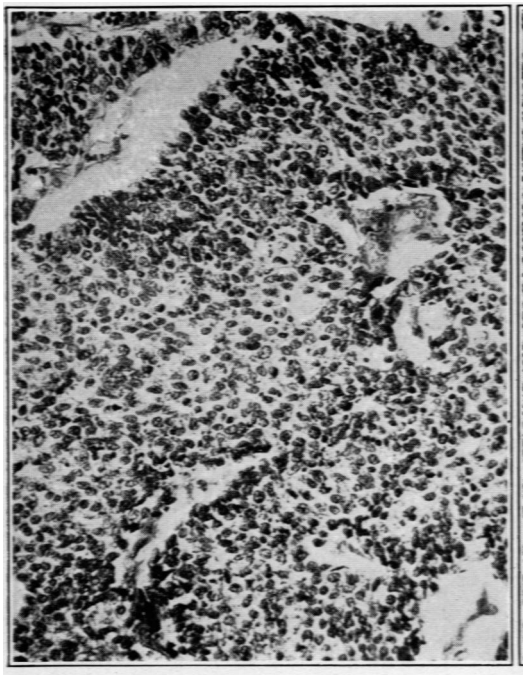
PLATE 119

FIG. 5. Spindle cells and round cells in small cell carcinoma in lung. Note shrunken connective tissue trabeculae. Hematoxylin and eosin. Green filter. × 200.

FIG. 6. Same tumor as in Fig. 5, stained by Bielschowsky-Foot method. Note absence of reticulum in the tumor nodules. Orange filter. × 200.

FIG. 7. Hepatic metastasis of small cell tumor of lung. Hematoxylin and eosin. Green filter. × 200.

FIG. 8. Area near that shown in Fig. 7 stained by Bielschowsky-Foot method. Note absence of reticulum in tumor nodules. Orange filter. × 200.



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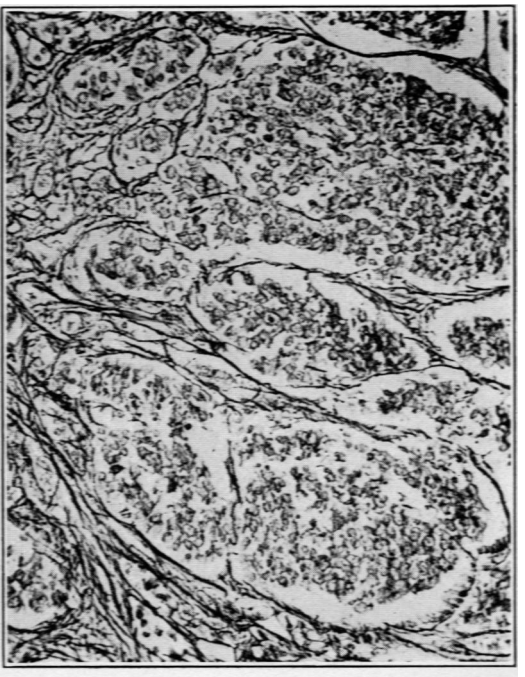

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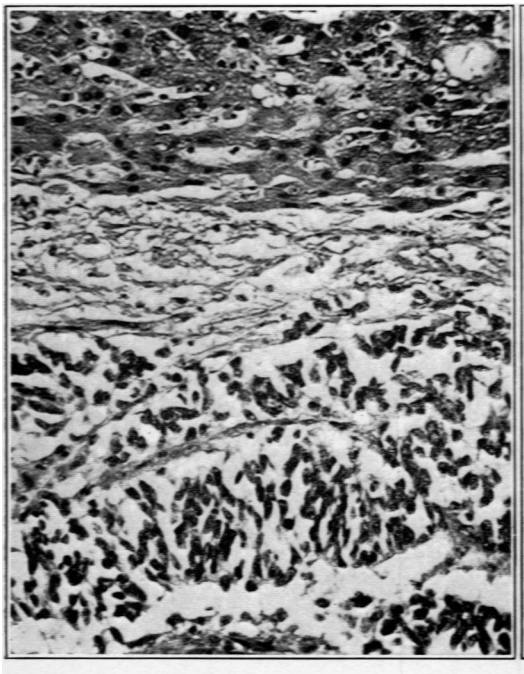

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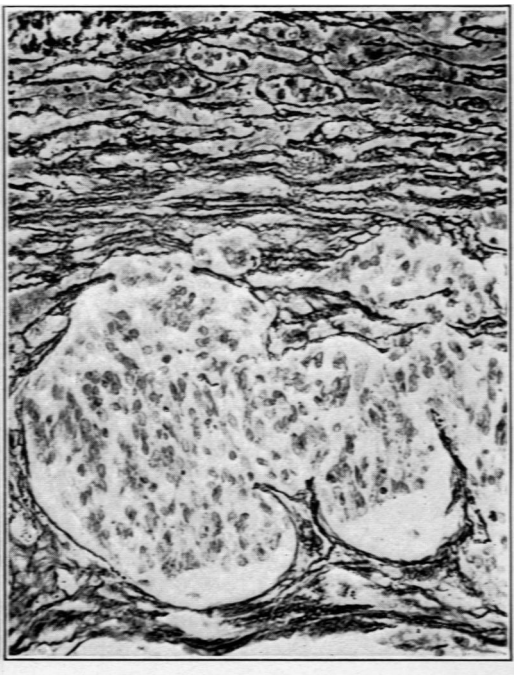

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Karsner and Saphir

Small Cell Carcinomas of the Lung